IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	: 10/552,134	Confirmation No. 7198
Applicant:	: Irina Velikyan	
Filed	: Sept. 14, 2006	
TC/A.U.	: 1618	
Examiner:	: Melissa Jean Perreira	
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Customer No.	: 36335	

Mailstop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Dear Sir:

Applicants request a pre-appeal conference in the above-identified application. A Notice of Appeal is filed concurrently herewith.

The following responds to the Final Office Action mailed November 18, 2010, rejecting the pending claims under 35 U.S.C. § 103(a) over various combinations of the following references: (1) Griffiths (WO 03/059397); (2) Yngve [Int.Diss.Abs., 62 (2001)]; (3) Bottcher (U.S. Patent No. 5,439,863); (4) Lidstrom [Tet.Lett., 57, 9225-9283 (2001)]; (5) Maier-Borst (GB 2056471 A); and (6) Wheaton [Industr.Eng.Chem., 43, 1088-1093 (1951)].

I. *Introduction*

Claim 1 is directed to a method of producing a radiolabelled gallium complex. The claim requires that the complex be in a form suitable for use in PET or SPECT radiopharmaceutical imaging. The method comprises reacting a Ga^{3+} radioisotope in a suitable solvent with a macrocyclic bifunctional chelating agent. The macrocyclic bifunctional chelating agent is linked to a targeting vector selected from the group consisting of proteins, glycoproteins, lipoproteins, polypeptides, glycopolypeptides, lipopolypeptides, peptides, glycopeptides, lipopeptides, carbohydrates, nucleic acids, oligonucleotides or small organic molecules. The reaction is carried out using microwave activation at 80 to 120 W for 20 s to 2 min.

For the reasons set forth in greater detail below, Applicants submit that the one of ordinary skill in the art would not look to the teachings of Bottcher to produce a radiolabelled gallium complex in a form that is **suitable for** PET or SPECT radiopharmaceutical imaging, as presently claimed. And, Applicants respectfully submit that, without Bottcher, the Patent Office's *prima facie* case of obviousness against the pending claims fails.

II. *Bottcher Seeks to Make Insoluble Complexes*

Botcher's stated goal is to make "complexes having low solubility, particularly such with a high ligand number or mixed coordinated metal complexes which are precipitated with a nearly quantitative yield . . . ." Bottcher at col. 3, lines 23-37. At various other points Bottcher reiterates that goal. *See, e.g.*, col. 3, lines 45-49; col. 3, line 64 – col. 4 line 2; col. 5, line 63 – col. 6, line 2; col. 6, lines 3-8; col. 6, lines 16-22; Examples 1 to 4; and claim 1, which refers to "recovering the product in fine crystalline form." Bottcher's complexes are designed to be insoluble in a variety of solvents, including 3:2 methanol/water (Example 1); 1:1 ethanol/water (Example 2); and 1:1 acetone/water (Example 3).

In contrast, the radiolabelled gallium complexes made by the claimed method are meant to be soluble, particularly in water. After all, the radiolabelled gallium complexes made by the claimed method are meant to be administered to human subjects so that PET or SPECT radiopharmaceutical imaging can be performed on those subjects. It is the inherent aqueous solubility of the radiolabelled gallium complexes made by the claimed method that makes them suitable for PET or SPECT radiopharmaceutical imaging. If the radiolabelled gallium complexes made by the claimed method were insoluble, they would not be suitable for PET or SPECT radiopharmaceutical imaging.

III. *Bottcher Uses Harsh Conditions That Would Not Yield Complexes Suitable for PET or SPECT Radiopharmaceutical Imaging*

The Bottcher method uses conditions that one of ordinary skill in the art would expect would have serious deleterious effects on the proteins, glycoproteins, lipoproteins, polypeptides, glycopolypeptides, lipopolypeptides, peptides, glycopeptides, lipopeptides, carbohydrates, nucleic acids, oligonucleotides or small organic molecules that are contained in the radiolabelled gallium complexes made by the claimed method. For example, to make his complexes, Bottcher

uses "inorganic auxiliary bases" such as NaOH, KOH, $Ca(OH)_2$, $Mg(OH)_2$ or basic salts, such as sodium acetate, sodium carbonate or potassium carbonate, sodium bicarbonate, $CaCO_3$. Bottcher at col. 3, lines 23-37. It is these "auxiliary bases" and/or "basic salts" that help promote the insolubility, and accelerate the precipitation, of Bottcher's metal complexes.

In addition, Bottcher employs "high energy input," brought about primarily by "the effect of high shear forces which occur with an extremely high stirrer speed . . . ." Bottcher at col. 3, lines 38-43; *see also* Examples 3 and 4, where the reaction mixture is stirred at 500 rpm and 1000 rpm, respectively. The "high energy input[(s)]" that Bottcher uses include stirring, ultrasound, microwaves or even "a laser beam." *Id.* at lines 43-45. The function that the "high energy input" serves in Bottcher is the acceleration of "the formation of the complexes themselves as well as of the precipitating crystals." *Id.* at lines 38-43.

Applicants submit that the use of "inorganic auxiliary bases," by themselves, would have serious deleterious effects on the proteins, glycoproteins, lipoproteins, polypeptides, glycopolypeptides, lipopolypeptides, peptides, glycopeptides, lipopeptides, carbohydrates, nucleic acids, oligonucleotides or small organic molecules that are contained in the radiolabelled gallium complexes made by the claimed method. For example, sodium hydroxide would likely denature and/or hydrolyze the proteins, glycoproteins, lipoproteins, polypeptides, glycopolypeptides, lipopolypeptides, peptides, glycopeptides, and lipopeptides contained in the radiolabelled gallium complexes made by the claimed method. Sodium hydroxide would also likely hydrolyze the carbohydrates, nucleic acids and oligonucleotides. Finally, "inorganic auxiliary bases" would likely cause the hydrolysis of any radiolabelled gallium complex made by the claimed method. After all, the chemical bonds that link the macrocyclic bifunctional chelating agent to the targeting vector (i.e., proteins, glycoproteins, lipoproteins, polypeptides, glycopolypeptides, lipopolypeptides, peptides, glycopeptides, lipopeptides, carbohydrates, nucleic acids, oligonucleotides or small organic molecules) are amide bonds and would likely be hydrolyzed by such "inorganic auxiliary bases."

Applicants submit that the use of "basic salts" would have deleterious effects, similar to those the "inorganic auxiliary bases" might have on the proteins, glycoproteins, lipoproteins, polypeptides, glycopolypeptides, lipopolypeptides, peptides, glycopeptides, lipopeptides, carbohydrates, nucleic acids, oligonucleotides or small organic molecules that are contained in the radiolabelled gallium complexes made by the claimed method.

Finally, at least the high shear stirring and ultrasound "high energy input" used by Bottcher to generate his complexes would likely destroy either the entire complex or at least the proteins, glycoproteins, lipoproteins, polypeptides, glycopolypeptides, lipopolypeptides, peptides, glycopeptides, lipopeptides, carbohydrates, nucleic acids, oligonucleotides or small organic molecules that are contained in the radiolabelled gallium complexes made by the claimed method.

In sum, it is Applicants' position that a radiolabelled gallium complex made using the combined teachings of Griffiths, Yngve, Bottcher, Lidstrom, Maier-Borst, and Wheaton, would not produce a radiolabelled gallium complex in a form **suitable for** PET or SPECT radiopharmaceutical imaging. For the claimed radiolabelled gallium complexes to be suitable for PET or SPECT radiopharmaceutical imaging they must be soluble and the integrity of the proteins, glycoproteins, lipoproteins, polypeptides, glycopolypeptides, lipopolypeptides, peptides, glycopeptides, lipopeptides, carbohydrates, nucleic acids, oligonucleotides or small organic molecules contained in the complex cannot be compromised.

Applicants respectfully submit that the Applicants respectfully submit that the 35 U.S.C. § 103 rejections over the art of record can not stand for the reasons set forth above. Accordingly, Applicants respectfully request withdrawal of these rejections.

Respectfully submitted,

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